

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application: **(AS ON AMENDED SHEET(S) UNDER ARTICLE 19 RECEIVED BY THE IB ON 8 JULY 2004)**

Claims 1 – 40. (Cancelled)

41. (new) A method of clearing intracellular aggregate-prone proteins in the prophylaxis of a protein conformational disorder in an individual comprising:
stimulating autophagy activity in the individual,
wherein said stimulation promotes clearance of said proteins.

42. (new) The method of claim 41 wherein the protein conformational disorder is characterised by intracellular aggregation of said proteins.

43. (new) The method of claim 41 comprising administering an autophagy-inducing agent to said individual.

44. (new) The method of claim 43 wherein the autophagy-inducing agent is an mTOR inhibitor.

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45. (new) The method of claim 44 wherein the autophagy-inducing agent is a rapamycin macrolide.

46. (new) The method of claim 45 wherein the rapamycin macrolide is rapamycin.

47. (new) The method of claim 45 wherein the rapamycin macrolide is a rapamycin analogue.

48. (new) The method of claim 47 wherein the rapamycin analogue is selected from the group consisting of CCI-779, 40-O-(2-hydroxy)ethyl-rapamycin, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxyethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-rapamycin and 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

49. (new) The method of claim 41 wherein the disorder is a codon reiteration mutation disorder.

50. (new) The method of claim 49 wherein the disorder is a polyQ expansion disorder.

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51. (new) The method of claim 50 wherein the polyQ expansion disorder is selected from the group consisting of Huntington's disease, spinocerebellar ataxias types 1, 2, 3, 6, 7, and 17, Kennedy's disease and dentatorubral-pallidoluysian atrophy.

52. (new) The method of claim 49 wherein the disorder is a polyA expansion disorder.

53. (new) The method of claim 41 wherein the disorder is an α -synucleinopathy.

54. (new) The method of claim 53 wherein the disorder is selected from the group consisting of Parkinson's disease, LB variant Alzheimer's disease and LB dementia.

55. (new) The method of claim 41 wherein the disorder is a prion disorder.

56. (new) The method of claim 55 wherein the prion disorder is CJD.

57. (new) A method of identifying an agent useful in the treatment of a protein conformational disorder comprising;

contacting a mammalian cell with a test compound; and,

determining the autophagy activity of said cell,

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wherein an increase in autophagy activity in the presence of said compound is indicative that the compound is a candidate agent for use in the treatment of a protein conformational disorder.

58. (new) The method of claim 57 wherein the cell comprises a heterologous nucleic acid encoding an aggregation-prone polypeptide.

59. (new) The method of claim 58 wherein said heterologous nucleic acid is operably linked to an inducible promoter.

60. (new) The method of claim 59 comprising expressing said nucleic acid and stopping said expression, prior to contacting the mammalian cell with the test compound.

61. (new) The method of claim 57 comprising modifying the compound to optimise the pharmaceutical properties thereof.

62. (new) The method of claim 57 comprising formulating the test compound into a pharmaceutical composition.

63. (new) A method of producing an agent for the treatment of a protein conformational disorder comprising;

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modifying rapamycin to produce a rapamycin derivative; and; determining the autophagy inducing activity of said derivative.

64. (new) The method of claim 63 comprising determining the ability of said derivative to inhibit mTOR.

65. (new) The method of claim 64 comprising determining the ability of said derivative to enhance the clearance of intracellular aggregate-prone proteins.

66. (new) A method of treating a polyQ expansion disorder in an individual comprising:

stimulating autophagy activity in the individual,

wherein the polyQ expansion disorder is selected from the group consisting of spinocerebellar ataxias types 1, 2, 3, 6, 7, and 17, Kennedy's disease and dentatorubral-pallidoluysian atrophy.

67. (new) A method of treating a polyA expansion disorder in an individual comprising:

stimulating autophagy activity in the individual.

68. A method of treating an α -synucleinopathy in an individual comprising:
stimulating autophagy activity in the individual

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wherein the α -synucleinopathy is selected from the group consisting of LB variant Alzheimer's disease and LB dementia.

69. (new) A method of treating a prion disorder in an individual comprising:
stimulating autophagy activity in the individual
70. (new) The method of claim 66 comprising administering an autophagy-inducing agent to said individual.
71. (new) The method of claim 70 wherein the autophagy inducing agent is an mTOR inhibitor.
72. (new) The method of claim 70 wherein the autophagy-inducing agent is a rapamycin macrolide.
73. (new) The method of claim 72 wherein the rapamycin macrolide is rapamycin.
74. (new) The method of claim 72 wherein the rapamycin macrolide is a rapamycin analogue.
75. (new) The method of claim 74 wherein the rapamycin analogue is selected from the group consisting of CCI-779, 40-O-(2-hydroxy)ethyl-rapamycin, 32-deoxo-

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rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxyethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-rapamycin and 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

76. (new) The method of claim 67 comprising administering an autophagy-inducing agent to said individual.

77. (new) The method of claim 76 wherein the autophagy inducing agent is an mTOR inhibitor.

78. (new) The method of claim 76 wherein the autophagy-inducing agent is a rapamycin macrolide.

79. (new) The method of claim 78 wherein the rapamycin macrolide is rapamycin.

80. (new) The method of claim 78 wherein the rapamycin macrolide is a rapamycin analogue.

81. (new) The method of claim 80 wherein the rapamycin analogue is selected from the group consisting of CCI-779, 40-O-(2-hydroxy)ethyl-rapamycin, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-

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hydroxyethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-rapamycin and 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

82. (new) The method of claim 68 comprising administering an autophagy-inducing agent to said individual.

83. (new) The method of claim 82 wherein the autophagy inducing agent is an mTOR inhibitor.

84. (new) The method of claim 82 wherein the autophagy-inducing agent is a rapamycin macrolide.

85. (new) The method of claim 84 wherein the rapamycin macrolide is rapamycin.

86. (new) The method of claim 84 wherein the rapamycin macrolide is a rapamycin analogue.

87. (new) The method of claim 86 wherein the rapamycin analogue is selected from the group consisting of CCI-779, 40-O-(2-hydroxy)ethyl-rapamycin, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxyethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-rapamycin and 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

88. (new) The method of claim 69 comprising administering an autophagy-inducing agent to said individual.

89. (new) The method of claim 88 wherein the autophagy inducing agent is an mTOR inhibitor.

90. (new) The method of claim 88 wherein the autophagy-inducing agent is a rapamycin macrolide.

91. (new) The method of claim 90 wherein the rapamycin macrolide is rapamycin.

92. (new) The method of claim 90 wherein the rapamycin macrolide is a rapamycin analogue.

93. (new) The method of claim 92 wherein the rapamycin analogue is selected from the group consisting of CCI-779, 40-O-(2-hydroxy)ethyl-rapamycin, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxyethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-rapamycin and 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.